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Dopaminergic receptor agents and the basal ganglia

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Chapter 1

The basal ganglia

1.1. Anatomy

The basal ganglia represent a number of subcortical nuclei that are closely arranged in the midbrain. The basal ganglia include the caudate nucleus, putamen, nucleus accumbens, globus pallidus, substantia nigra and subthalamic nucleus. The caudate nucleus, putamen and nucleus accumbens are very similar in internal structure and are often referred to as the neostriatum or simply striatum.

The functional significance of the basal ganglia is illustrated by the massive input from the cortex, thalamus and substantia nigra pars compacta to the striatum (fig. 1). The output from the striatum is almost exclusively restricted to other structures of the basal ganglia. The external and internal segments of the globus pallidus and the substantia nigra pars reticulata receive the main projections from the striatum. The external segment of the globus pallidus projects mainly to the subthalamic nucleus, which projects back to the globus pallidus and to the substantia nigra. The internal segment of the globus pallidus (the entopenducular nucleus in rodents and cats) and the substantia nigra pars reticulata project outside the basal ganglia to thalamic and brainstem nuclei, therefore providing the main output pathways to other brain areas. Efferents of the thalamus project back to cortical structures, completing a feedback circuitry (review: Wilson, 1990).

A commonly accepted classification of the striatum is the distinction between a ventromedial region (the 'limbic' striatum) and a dorsolateral region (the 'non-limbic' striatum). In this thesis, the dorsolateral part of the striatum will be focussed on since most experiments have been performed in this structure. The ventromedial striatum will be discussed briefly. The ventral striatum is organized in a manner similar to the dorsal striatum projecting mainly to the ventral part of the globus pallidus and the substantia nigra.

Although several structures, including the subthalamic nucleus, substantia nigra and globus pallidus, receive innervations from areas outside the basal ganglia, most input enters the system at the level of the striatum. The striatum, therefore, is of central importance in the functioning of the basal ganglia.

1.2. Striatal neuronal morphology

1.2.1. Medium-sized spiny neurons

The medium-sized spiny neurons constitute 96% of all striatal neurons (Kemp and Powell, 1971a). They are characterized by their medium sized perikarya (10-20 μm in diameter) from which dendrites radiate that fill a roughly spheric volume with a radius

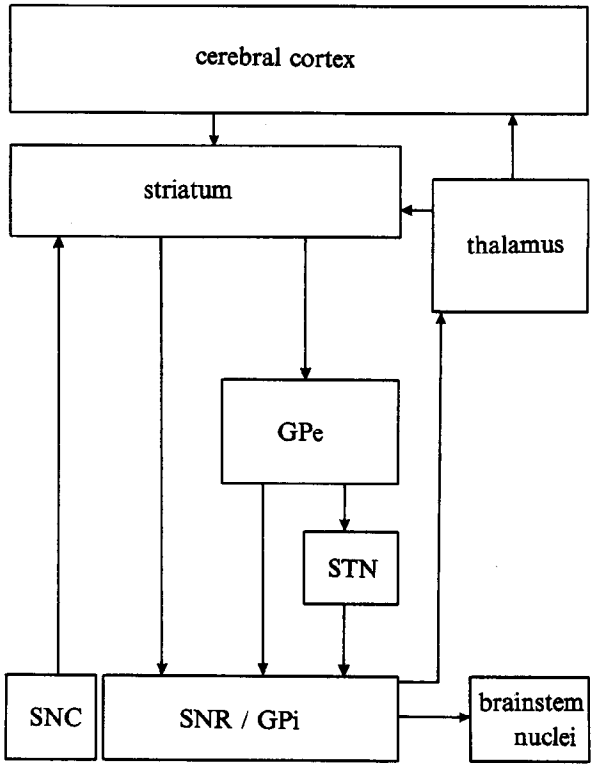

Figure 1. Schematic diagram of the most important pathways of the basal ganglia. Abbreviations: SNC, substantia nigra pars compacta; SNR, substantia nigra pars reticulata; GPe, external segment of the globus pallidus; GPi, internal segment of the globus pallidus; STN, subthalamic nucleus.

of 300-500 μm (DiFiglia et al., 1976; Wilson and Groves, 1980). The cell body and the proximal parts of the dendrites are usually smooth, while the more distal parts (after 30 μm) are densely laden with spinous processes. By intracellular injection of horseradish peroxidase (HRP) Chang et al. (1981) have identified axons of medium-spiny neurons that arborize within the globus pallidus. A combination of Golgi impregnation and retrograde transport of HRP from the substantia nigra revealed the existence of striatonigral axons of medium-spiny neurons (Somogy and Smith, 1979). Medium-spiny neurons not only extend long projecting axons to the globus pallidus and the substantia nigra, they also give off extensive collaterals within the striatum that form classical symmetrical synapses with medium-spiny neurons themselves and other striatal neurons (Somogyi et al., 1981; Wilson and Groves, 1980). Immunocytochemical techniques have demonstrated that the medium-spiny neurons contain glutamate decarboxylase (GAD), which is the synthetic enzyme for gamma-aminobutyric acid (GABA) (e.g. Ribak et al.,

1979). In addition to GABA, various peptides are present in particular subsets of cells (see 1.4).

The medium-spiny neurons provide the basic framework of the striatal circuitry. The various projections that terminate on medium-spiny neurons can be categorized in symmetrical and asymmetrical membrane specializations. The asymmetrical synapses make contact almost exclusively with the dendritic spines, whereas the symmetrical synapses occur on all parts of the neuron, i.e. dendritic spines and shafts, cell bodies and axon initial segments. It is characteristic of the distribution of synaptic inputs on different parts of the medium-spiny neuron that extrinsic information is received and probably processed in distal regions of the neuron, while local information is received predominantly on the proximal dendrites and perikarya of medium-spiny neurons, suggesting that the local input has a modulatory role (Smith and Bolam, 1990).

1.2.2. Medium-sized aspiny interneurons

The medium-sized aspiny interneurons have rounded somata and smooth or sparsely spinous dendrites. They represent about 1% of the striatal cell population and are classified as interneurons because of the local axonal arborization (DiFiglia et al., 1976). The neurotransmitter of the medium-sized aspiny neurons is GABA (Bolam et al., 1983). Both symmetrical and asymmetrical synapses are found on the aspiny neurons (DiFiglia et al. 1980; Tagaki et al., 1984). GABA-ergic interneurons themselves and medium-spiny neurons represent the major input and targets of GABA-ergic interneurons (Takagi et al., 1984).

1.2.3. Giant aspiny interneurons

The giant aspiny interneurons represent less than 2% of all striatal cells (Bishop et al., 1982; Chang and Kitai, 1982; Difiglia and Carey, 1986). These cells are probably the largest neurons in the striatum. They have an elongated soma up to 50-60 μm in length (diameter 15-25 μm) with long smooth dendrites. The axon arborization is typically associated with interneurons. The neurotransmitter of the giant aspiny neurons is acetylcholine (Phelps et al., 1985). The input to the cholinergic neurons consists of boutons forming both symmetrical and asymmetrical membrane specializations (Bolam, 1984; Chang and Kitai, 1982; Tagaki et al., 1984).

1.2.4. Somatostatin-positive interneurons

The somatostatin-positive interneurons are medium-sized, with long aspiny dendrites and reveal somatostatin immunoreactivity (DiFiglia and Aronin, 1982; Takagi et al., 1983). The axon arborizes close to the cell body, indicating that these neurons are probably interneurons as well. Asymmetrical and symmetrical varicosities have been found on these neurons.

1.3. Afferent projections of the striatum

1.3.1. Corticostriatal pathway

The direct projection from the cerebral cortex provides one of the principal afferent systems to the striatum. It is well established that all major regions of the cerebral cortex project onto the striatum (e.g. McGeorge and Faull, 1989). The entire corticostriatal projection is topographically organized (Selemon and Goldman-Rakic, 1985; McGeorge and Faull, 1989). The corticostriatal neurons are thought to use glutamate as a neurotransmitter (Divac et al., 1977; Kim et al., 1977; McGeer et al., 1977). They exert an excitatory influence (review: Feger et al., 1979; Kitai, 1981) predominantly on medium-spiny neurons (Kemp and Powell, 1971b; Hattori et al., 1979). The asymmetric synapse is the characteristic synaptic type formed by afferents from the cerebral cortex (Kemp and Powell, 1971b). Stimulation of the cerebral cortex evokes a large-amplitude excitatory postsynaptic potential (the sum of action of many synapses) in the medium-spiny neurons in the striatum (Wilson et al., 1982, 1983). Cerebral cortical ablation studies suggest that the input from the cerebral cortex accounts more for the variability in firing rather than the maintenance of tonic firing of striatal neurons (Aldridge et al., 1990).

1.3.2. Thalamostriatal pathway

The thalamostriatal projections originate predominantly from the intralaminar and midline thalamic cell groups (e.g. Nauta et al., 1974; Veening et al., 1980; Parent et al., 1983). For most of these nuclei their projection to the striatum is topographically organized (Beckstead, 1984; Berendse and Groenewegen, 1990). The thalamostriatal projections are excitatory in nature (Kitai et al., 1976; Wilson et al., 1983) probably using an excitatory amino acid (glutamate or aspartate) as a neurotransmitter (Fuller et al., 1987; Kaneko and Mizuno, 1988), although acetylcholine has also been mentioned as a candidate for some of the thalamostriatal neurons (e.g. Nieoullon et al., 1985). Projections from the thalamic nuclei terminate on medium-spiny neurons, establishing predominantly asymmetrical synapses on the head of dendritic spines (e.g. Kemp and Powell, 1971b). One area of the thalamus, the parafascicular nucleus, however, establishes asymmetric synaptic contact with the dendritic shafts of a morphologically distinct type of medium-spiny neurons (Dubé et al., 1988). Stimulation of the thalamus produces effects that are very similar to those of cortical stimulation (Wilson et al., 1983).

1.3.3. Nigrostriatal pathway

Neurons originating from the substantia nigra pars compacta project throughout the striatum, with the exception of the ventral zone, which is sparsely innervated (Beckstead et al., 1979). These neurons use dopamine as a neurotransmitter (review:

Moore and Bloom, 1978), although a small portion of the nigrostriatal neurons has been found to be non-dopaminergic (e.g. Matsuda et al., 1987). In some of the dopaminergic neurons the peptide cholecystokinin is colocalized (Studler et al., 1982). The dopaminergic projections may terminate on all striatal cell types, but predominantly on medium-spiny striatal neurons. It has been shown that symmetrical synapses are formed on dendritic shafts, somata and the neck of dendritic spines of these GABA-ergic neurons (Freund et al., 1984). Thus, dopamine can exert both a general influence on these neurons as well as a modulatory effect since the dopaminergic input to the neck of dendritic spines can modulate the excitatory input to the head of the same spine before reaching the dendritic shaft.

1.3.4. Other afferents

Projections to the striatum originating from the amygdala (Kelley et al., 1982), hippocampus (Kelley and Domesick, 1982), dorsal raphe (Pasik et al., 1981) and ventral tegmental area (Beckstead et al., 1979) have been described. These afferents originate in so-called limbic structures or in brainstem structures embedded in the circuitry of the limbic system. They do not innervate the entire striatum since the dorsolateral striatum is largely avoided (Kelley et al., 1982). Innervations from limbic cortical areas show a similar arrangement.

1.4. Efferent projections of the striatum

1.4.1. Striatopallidal pathway

Striatofugal fibers maintain an orderly radial arrangement (Nauta and Mehler, 1966). The topographical organization, strikingly present in the corticostriatal projections, is likewise visible in the striatopallidal pathway. Striatofugal fibers terminate both in the external and internal segment of the globus pallidus (Nauta and Domesick, 1984) (fig. 2). Immunocytochemical studies have shown that both projections contain GABA as a neurotransmitter (Fonnum et al., 1978; Nagy et al., 1978). These neurons, however, differ in peptide content, which suggests that the two pallidal segments are innervated by separate striatal cells (Nauta and Domesick, 1984). Enkephaline is mainly colocalized in neurons terminating in the external segment of the globus pallidus (Cuello and Paxinos, 1978; Gerfen and Young, 1988), while substance P and dynorphin predominate in the GABA-ergic neurons projecting to the internal segment of the globus pallidus (Jessell et al., 1978; Kanazawa et al., 1980). The GABA-ergic striatopallidal neurons exert an inhibitory influence on target structures (Yoshida et al., 1972). Modulation of this response may be produced by the colocalized peptides. A characteristic low rate of firing is exhibited by these striatal neurons (Wilson and Groves, 1981). Therefore, under basal conditions, the pallidal neurons are not severely inhibited. In addition to projecting to the target structures, the striatal projection-neurons have local axon collaterals that are

distributed within the locale of their dendritic arbor (Wilson and Groves, 1980; Somogyi et al., 1981). The collaterals form symmetrical synapses with, for example, their own cell type, the medium-spiny neurons. The synapses on dendritic spines are most often situated on the neck of a spine that also receives excitatory input on the head region (Gerfen, 1988).

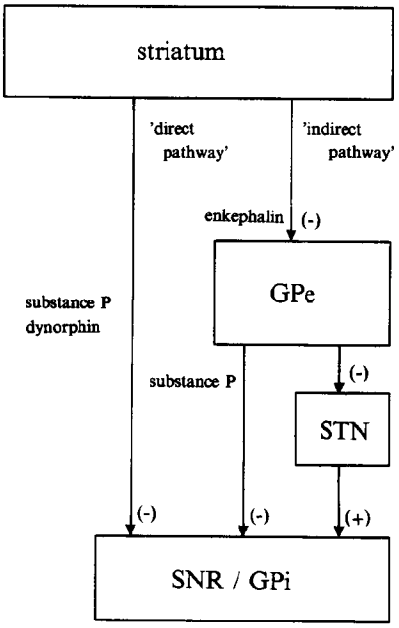

Figure 2. Schematic diagram of the striatopallidal and striatonigral pathways with the most prominent colocalized neuropeptides.

1.4.2. Striatonigral pathway

Striatal GABA-ergic neurons topographically project to the substantia nigra reticulata, giving rise to massive convergence of information (Grovofa, 1975; Hattori et al., 1973; Brownstein et al., 1977; Nauta and Domesick, 1984). Considering their peptide content, these striatonigral fibers resemble those striatal neurons that innervate the internal segment of the globus pallidus, as substance P and dynorphin are the predominantly colocalized peptides (Brownstein et al., 1977; Gerfen and Young, 1988) (fig. 2). Moreover, it is thought that the internal segment of the globus pallidus is related more to the substantia nigra reticulata than to the external segment of the globus pallidus. The internal segment of the globus pallidus and the substantia nigra reticulata together are often considered as the output structure of the basal ganglia. The three striatal projections originate in separate cell populations in primates and cats. In rats, however, part of the striatofugal neurons have been reported to send axon collaterals to both the globus pallidus and the substantia nigra reticulata (review: Parent, 1990). The described characteristics of striatal cells (see 1.4.1) also hold for the striatonigral neurons.

In addition to the direct striatal GABA-ergic innervation, there are two indirect

innervations from the striatum to the substantia nigra reticulata via the external segment of the globus pallidus. One indirect innervation is formed by GABA-ergic pallidal output neurons which inhibit the excitatory subthalamic input to the internal segment of the globus pallidus and the substantia nigra (review: Albin et al., 1989). The other one is established by an inhibitory GABA-ergic pallidonigral pathway (Smith and Bolam, 1989). These neurons originate in the globus pallidus in rodents or in the external segment of the globus pallidus in primates (Smith and Bolam, 1989; Parent, 1990), receive monosynaptic input from the striatum (Todderdell et al., 1984) and contain substance P (Bolam and Smith, 1990). Convergence of synaptic inputs from striatal and pallidal neurons onto a single output neuron both in the substantia nigra and in the entopeduncular nucleus has been reported recently (Smith and Bolam, 1990; 1991). Thus, these indirect pathways give rise to a disinhibitory next to an inhibitory innervation from the striatum.

1.5. The mosaic organization of the striatum

The striatum is composed of two distinct compartments, the patches (or striosomes) and matrix, that are arranged in a mosaic fashion (Graybiel and Ragsdale, 1978; Gerfen et al., 1985). These compartments show differences in the distribution of neurochemical markers. In the patch compartment for instance there is very little acetylcholinesterase present, while it is rich in μ-opiate receptors (Herkenham and Pert, 1981). In the matrix there is a high concentration of calcium binding protein and somatostatin (Gerfen et al., 1985; 1987a). Afferent fibers of cortical origin (Donoghue and Herkenham, 1986; Gerfen, 1989), but also thalamic afferents (Herkenham and Pert, 1981) and dopaminergic afferents (Gerfen et al., 1987b; Feigenbaum-Langer and Graybiel, 1989) respect these tissue compartment boundaries. Some areas project exclusively to the patches, others to the matrix. The patches are sometimes referred to as limbic islands, because limbic structures largely project onto the patches (Graybiel, 1990). All striatal cell types seem to be present in both compartments (Wilson, 1990). The medium-spiny neurons in either patch or matrix keep their dendritic and axonal field within the compartment boundaries (Herkenham et al., 1984; Penny et al., 1988). The segregation that is apparent for the input to the striatum, seems also to account for the striatal output. Striatonigral neurons originating in patches project to the substantia nigra pars compacta, whereas those in the matrix terminate in the substantia nigra pars reticulata (Gerfen, 1984; Gerfen et al., 1987b). The striatopallidal projections appear mainly to originate from the matrix (Gimenez-Amaya and Graybiel, 1991). The segregated input into and out of patch and matrix compartments of the striatum seem to establish parallel and independent pathways through the basal ganglia (Wilson, 1990). The division, however, is not absolute. Dendrites of giant cholinergic interneurons and somatostatin-positive interneurons appear to span patch-matrix boundaries (Gerfen, 1985; Penny et al., 1988). These interneurons may play a role in the intercommunication between patch and matrix compartments. The mosaic organization of the striatum is likely to have functional implications, but these remain to be elucidated.

1.6. Basal ganglia function

The medium-spiny neurons provide the basic framework of striatal circuitry. These neurons, which are silent or occasionally active under basal conditions (Wilson and Groves, 1981) are activated by temporal coincidence of convergence of excitatory input from, for example, cortical or thalamic structures (Groves, 1983). By activating the striatal output neurons, an inhibitory effect is exerted on pallidal and nigral neurons, but also a disinhibitory effect on nigral neurons is induced via the indirect striatonigral tract (review: Albin et al., 1989). These nigral output neurons of the basal ganglia are GABA-ergic and responsible for a strong synaptic inhibition on thalamic and brainstem nuclei (Uno et al., 1978; Chevalier et al., 1981; Hikosaka and Wurtz, 1983). Inhibition exerted by the usually silent striatal neurons during the brief episodes of firing induces a short decrease in tonic firing rate in the pallidal and nigral cells, temporary releasing thalamus and brainstem cells from tonic inhibition, allowing convergent excitatory inputs to control cell firing (Delong et al., 1984) (fig. 3). This cascade of events indicates that disinhibition is the basic process for the expression of striatal functions. The information that is sent from the striatum should be regarded as a gating signal, enabling thalamic and brainstem circuits to become active (Chevalier and Deniau, 1990).

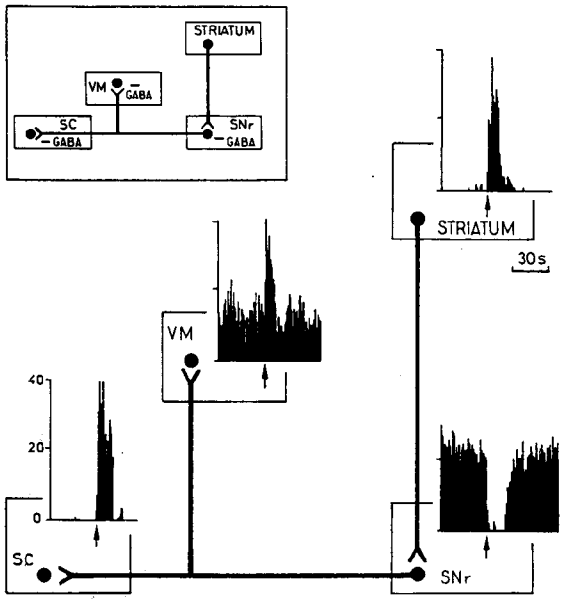

Figure 3. Anatomico-physiological organization of the striatonigrofugal pathways to the ventromedial thalamic nucleus (VM) and to a brainstem nucleus, the superior colliculus (SC). These circuits are composed of two serial GABA-ergic inhibitory links (see inset). In the main diagram, frequency histograms illustrate the sequence of electro-physiological events underlying the disinhibitory influence of the striatum. A striatal spike discharge, evoked by local application of glutamate (50nl; 30μM), readily induces a clearcut silencing of the tonically active nigral neurons (SNR). Released from the potent nigral inhibition, collicular and thalamic cells are vigorously discharged. Calibration of spike frequency is given in spikes per second. The arrow in each histogram indicates the onset of glutamate injection in the striatum (Chevalier and Deniau, 1990; with permission of Elsevier Science Publishers)

An important role for the dopaminergic input from the midbrain in the operation of the described network has been postulated. Although conflicting data exist, a lot of evidence points to an inhibitory effect of dopamine on striatal neurons projecting to the external segment of the globus pallidus and an excitatory effect of dopamine on neurons projecting to the internal segment of the globus pallidus and substantia nigra reticulata (for detailed information see 11.2.1). Globus pallidus neurons from the external segment project in turn onto the internal segment and substantia nigra reticulata output neurons (Albin et al., 1989; Smith and Bolam, 1989). By enhancing the transmission through the direct pathway and suppressing transmission through the indirect pathway (which counteracts the effect of the direct pathway), the dopaminergic nigrostriatal input seems to have the net effect of facilitating the activation of brainstem nuclei and augmenting positive feedback to cortical areas (DeLong, 1990). Dopamine is therefore thought to maintain not only the ongoing activities, but also to enable new activities to be initiated by overriding the ongoing ones (Penney and Young, 1983). In close relation to the nigrostriatal dopaminergic neurons, the cholinergic interneurons also play an important role in the modulation of striatal transmission (Stoof et al., 1992; Pickel and Chan, 1990, respectively). The intimate interaction between the two systems is clearly illustrated by the finding that dopamine, via D2 receptors, tonically inhibits striatal cholinergic neurons (review: De Boer, 1992). The effect of acetylcholine on striatal GABA-ergic neurons, however, is still a matter of discussion. GABA-ergic axon collaterals are believed to establish a lateral inhibitory network (Wilson and Groves, 1980), which may provide a means for sharpening the diffuse pattern of striatal input onto the striatal target system (Groves, 1983). The effect of striatal interneurons has not been extensively studied yet. They are expected to exert a local modulatory influence on the electrical activity of medium-spiny neurons (Wilson, 1990).

A close association is found between an increase in striatal neuronal activity and/or a decrease in pallidal and nigral output neuron activity and the occurrence of activities in a motor, sensory or associative context (Hikosaka and Wurtz, 1983; DeLong et al., 1984; Joseph and Boussaoud, 1985; Albin et al., 1989). As the disinhibition in the basal ganglia itself is not sufficient to trigger the behavioural activation, it is postulated that the basal ganglia would participate in enabling particular movements and in the control of their sequencing rather than in directly causing them to occur (Chevalier and Deniau, 1990).

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